Role of Innate Immunity in Pregnant Patients with Vulvovaginal Infections in the Development of Intrauterine Infection in the Newborn


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A total of 115 pregnant women were examined: 59 patients with opportunistic vulvovaginal infections and 56 without infection. Congenital immunity parameters (TLR-2, NF-κB, and IL-2 receptors in placental tissue) were studied by immunohistochemical methods. Realization of congenital infection was associated with activation of IL-6 receptors and TLR-2 in the placenta and an increase of NF-κB level. These changes seemed to reflect the strained status of congenital immunity and were responsible for the intensity of local inflammatory response.

Key Words: congenital immunity; Toll-like receptor 2; nuclear factor κB; interleukin 6 receptors; vulvovaginal infections

The incidence of vulvovaginal infections (bacterial vaginosis (BV), candidal and nonspecific vaginitis) in women of different age groups is increasing. The incidence of these infections in pregnant women varies from 10 to 41% [3-5,7]. Unfavorable effects of opportunistic vulvovaginal infections (OVI) on the course and outcome of pregnancy – high incidence of miscarriages, chorioamnionitis, the amniotic fluid infection syndrome, and postpartum proinflammatory complications – are proven [2,6,9].

The role of vaginal bacterial infections in triggering of the pathogenetic mechanisms of intrauterine infection (IUI), preterm labor, development of small-for-date fetuses (SDF) remains unclear; there is no universal opinion on the specific features of cellular and humoral immunity responsible for bacterial colonization [1,8].

We studied the role of congenital immunity factors (IL-6 receptors, TLR-2, NF-κB) in placental tissue in the development of IUI in the newborns.

MATERIALS AND METHODS

The study was carried out in 115 patients divided into 2 groups. Group 1 (the main) consisted of 59 patients with OVI, group 2 (control) included 56 patients without OVI. All patients signed informed consent to participation in the study. The patients’ ages varied from 18 to 41 years, median 31.4±0.5 and 28.4±0.5 years in groups 1 and 2, respectively.

Group 1 patients were characterized by higher incidence of chronic diseases of the ENT organs (by 40%; \( p<0.05 \)) and urinary system, in particular, chronic pyelonephritis and chronic cystitis (by 20 and 26%, respectively; \( p<0.05 \)). Study of the structure of gynecological morbidity showed significantly (\( p<0.05 \)) higher incidence of chronic endometritis (by 18%), chronic salpingo-oophoritis (by 20%), benign ovarian tumors (by 12%), infertility (by 16%), and cervicitis (by 54%). The course of pregnancy in patients of the main group was significantly more often aggravated by placental failure (4.8% cases vs. 0.9% in control group), oligoamnios (according to ultrasonic examination; 9.6 and 4.6%, respectively), and chronic fetal hypoxia (according to cardiotocography; 9.4 and 1.9%, respectively). Threatened abortions were 2-fold...
more incident in the main group in comparison with the control. The postpartum period in patients of the main group was significantly more often complicated by endometritis (2.2% vs. 0.3% in controls). Pregnancies eventuated in delivery of 115 infants. In the main group 45.4% infants were born healthy, in control group 55.5%. The mean number of diseases per unhealthy infant was 1.8 in the main group and 1.7 in control.

Group 1 patients were divided into 3 subgroups for complex morphological study of the placentas. Subgroup A included patients with BV, subgroup B included patients with BV and candidal vaginitis, and subgroup C included patients with BV and aerobic vaginitis. Histological studies were carried out on preparations stained by hematoxylin and eosin. Immunohistochemical studies were carried out on paraffin sections (3-4 μ) of the placenta using ready-to-use polyclonal rabbit antibodies to IL-6 receptors (Thermo Scientific), TLR-2 (Novus Biologicals), and NF-κB (AbD Serotec). The staining intensity in reactions with antigens was evaluated by a semiquantitativ method using an 8-point scale (0 points – no reaction, 8 points – intense reaction).

The data were statistically processed by Statistica 8.0 software. Shapiro–Wilk test, χ² test for 2×2 signs conjugation tables (for comparison of sign incidences in analyzed groups), Bonferroni’s correction (for higher reliability in repeated analysis of part of analyzed data). Comparative analysis of the mean trends was carried out using Student’s t test (by the results of testing for normality).

RESULTS

Clinical analysis of the course and outcome of pregnancy in patients with genital opportunistic infections and normal vaginal microbiocenosis showed a significantly higher incidence of obstetrical complications (threatened abortion, placental failure, endometritis) in pregnant patients with OVI. On the other hand, analysis of the incidence of neonatal diseases, including IUI, showed no appreciable difference between the groups. However, a trend to a higher incidence of IUI was traced in the newborns whose mothers suffered from vaginal infection (10.9 vs. 6.9% in control group). Pneumonia predominated in the structure of IUI.

Morphological studies of placentas showed that placental tissue corresponded to full-term pregnancy in both groups. The mean weights of placentas in the main and control groups were 507.5±21.9 and 508.5±22.4 g, respectively, its mean areas 282.6±32.2 and 296.2±34.9 cm², respectively. The structure of the placental membranes was normal in 57.9% observations in the main group and in 72.2% controls. The membranes were edematous and stratified in 34.2% pregnant women from the main group; fibrinoid depositions were also found. Amniocyte degeneration and desquamation were detected in one newborn; candidiasis concomitant with vaginosis were recorded in its mother during gestation.

Clinical microbiological study showed that aerobic vaginitis as a nosological entity with signs of inflammatory process was detected in 11.9% pregnant patients at first application. Aerobic vaginitis was diagnosed in 21.4% patients with pathological vaginal microbiota (BV in 56.1% cases, candidal vaginitis in 34.1%). Facultative anaerobic bacteria were detected in 59.8% pregnant patients with BV and in 54.3% patients with candidal vaginitis. Facultative anaerobic bacteria in high titers were found in 16.4% pregnant patients with BV and in 17% patients with candidal vaginitis. Hence, facultative anaerobic bacteria in high titers (more than 5 lg CFU/ml) were isolated from 36.4% pregnant patients with pathological vaginal microbiota. The main agents of aerobic vaginitis were group B streptococci (Streptococcus agalactiae – 62.2%), enterococci (48.7%), and escherichias (40.5%), isolated in monocultures and in associations. The same bacteria predominated in patients with BV and candidal vaginitis.

Studies of the placental histological preparations from the main group showed mainly compensatory adaptive changes. There were also signs of inflammation (lymphohistiocytic infiltration in the membranes, focal infiltration in perivascular tissue of the root villi with lymphoid elements and polymorphonuclear leukocytes).

Immunohistochemical studies showed that the mean levels of TLR-2 expression in the placental villous syncytiotrophoblast were higher in OVI patients than in controls. The intensity of reaction with IL-6 receptors were also significantly higher in the cyto- and syncytiotrophoblast, vascular endothelium, and macrophages in preparations from the main group. The level of expression of NF-κB (nonspecific intracellular signal receptor) was higher in the patients with infection.

Comparative analysis detected different levels of expression of immunohistochemical markers in pregnant patients of the main group, which depended on the microorganism spectra. The mean levels of TLR-2 expression in immunoreactive cells in the placental villous syncytiotrophoblast were higher in pregnant patients of subgroup C than in subgroups A and B. The reaction intensity in subgroup A (patients with BV) was similar to the parameter in the control and even lower in macrophages.

The highest expression of IL-6 receptors was found in placental villous macrophages, cyto- and syncytiotrophoblast, and vascular endothelium in subgroup B (pregnant patients with aerobic vaginitis).